With regard to other matters of the specification, applicants believe that the sequence numbers (Sequence I.D. Nos. 1-6) are adequately identified on page 10 of the specification as referring respectively to the Seq. I.D. Nos. 1-6 which follow and so should meet the requirements of Item 5 in the latest Official Action. Note that Seq. I.D. Nos. 2, 4 and 6 are given 3' to 5' on page 10 or 11, but are indicated in the conventional 5' to 3' direction in the sequence listing.

Applicants greatfully acknowledge the withdrawal of the rejection of claims 1-23 under 35 USC § 112, however, they remain of the opinion that the claims are unobvious and should also be allowed on the merits. In this respect, entry and consideration of the following additional remarks are respectfully requested.

The rejection of claims 1-3 and 5-23 under 35 USC 103(a) has been repeated. The Examiner still maintains that the claims are unpatentable over Donnelly et al. EP 0 532 090 A2 (issued Sept. 2, 1992), in view of Fawell et al. (PNAS 91: 1994), Murphy US 5,668,255 (issued Sept. 16, 1997, priority to June 27, 1991). Zimmerman et al. US 5,652,341 (issued July 29, 1997, priority to Dec. 4, 1992), Lowenadler et al. (Mol. Immunology 29:1195, 1992), Noguchi et al. (PNAS 3171, April 1994) and Roemer et al. PNAS(90:9252, 1993). The position of the Examiner in this regard is respectfully traversed.

EP 0 532 090 discloses PE as both the cell binding and translocating portion. the cell binding portion is not specific for particular cell types, as acknowledged by the Examiner. In

Fawell et al, the HIV TAT effectively acts as both binding and translocating domain. Thus, both documents use a portion with both cell binding and translocating activity without any suggestion of splitting these two functions or providing two separate portions from different sources with separate cell binding or translocating activity. There is no teaching of any desirability of targeting of specific cells in either document.

Moreover, there is no suggestion in these documents that the binding and translocation portions could be from different sources, and no motivation exists in the documents for altering the teachings of these documents such that the binding and translocation portions are from different sources.

With respect to an other aspect of the general rejection under the above art combinations, the Examiner seeks to combine Murphy et al with Zimmerman et al, EP 0 532 090 and Fawell et al in order to demonstrate that the elected species (anti-MHC II antibody-p53-HIV-TAT) is unpatentable. Applicants cannot agree as next explained.

Murphy et al `255 discloses hybrid molecules with binding and effector portions where the effector portion is a toxin or derived from a toxin. There is no suggestion that the hybrid molecules could be used for presenting peptides by MHC molecules or exerting an immunomodulatory effect.

Zimmerman et al discloses hybrid molecules with two binding portions and no translocation portion. The Examiner appears to consider that Zimmerman et al discloses a cellular binding portion that is specific for MHC classes I and II. On the contrary,

Zimmerman et al uses portions of MHC class I or II molecules as the binding portion. The portion of the MHC class I or II molecule binds to a T cell receptor on a T cell. There is no mention of a cellular binding portion that binds to a MHC class I or II molecule. Thus, Zimmerman et al does not teach a chimeric protein in which the cellular binding portion is specific for MHC class I or II. Further, the hybrid molecules are intended to remain on the surface of the cell to which they are bound and there is no suggestion that the hybrid molecules are internalized by a cell. There is no indication that binding of the chimeric protein to an antigen presenting cell is intended or desirable.

Murphy et al, for example, and Zimmerman et al are not concerned with related problems and the Examiner has not indicated any motivation to combine Zimmerman et al with Murphy et al or with Fawell et al or EP 0 532 090. Even if the documents were to be combined, a molecule of the claimed invention would be neither taught nor suggested. There is no indication that a cellular targeting portion taught by Murphy et al or Zimmerman et al could be used with a translocation portion as used in EP 0 530 090 or Fawell et al.

The Examiner also seeks to further combine the above-cited references with Lowenadler et al. In the response dated January 4, 1999 (Paper No. 4), it was argued that the IgG-binding Protein A domain is not a cellular binding portion. The Examiner appears to have misinterpreted this argument and appears to consider that the argument presented was that the Sta epitopes do not target a

particular cell type. The Examiner then appears to contend that StaZZ represent the IgG binding component (cellular binding portion). This appears to be incorrect: Sta is the heat-stable enterotoxin of E. coli and the IgG binding domain is ZZ. As argued previously, there is no cellular binding portion.

There is no indication that the molecules of Lowenadler et al are internalized by cells and therefore no indication that multiple copies of any immunogenic peptide would be of benefit in a chimeric polypeptide that is internalized.

In relation to Roemer et al, relating to a hybrid molecule comprising an estrogen receptor portion, the estrogen receptor is an intracellular protein, not a target cell surface component, as required by claims 1 and 2. Further, there is no demonstration of targeting of the hybrid molecule to cells, as the hybrid molecule is expressed in cells following the transfection of a construct encoding the hybrid molecule into the cells. The human estrogen receptor hormone binding portion does not target the chimeric protein to cells expressing estrogen receptors, as contended by the Examiner.

In view of the comments above concerning the hybrid molecules described in Zimmerman et al, applicants contend that the Examiner has not demonstrated a fusion protein comprising an immunogenic peptide and an anti-MBH cell targeting component in the art. Thus, even were there any motivation to combine teaching concerning fusion proteins comprising an immunogenic peptide and a translocating component with a fusion protein comprising an

immunogenic peptide and an anti-MHC cell targeting component, it still would not demonstrate that the latter fusion protein is taught in the prior art.

In response to the Examiner's comments concerning the efficiency of the p53-HIVtat-anti-MHC chimeric polypeptide, in comparison with the p53 peptide, in eliciting anti-p53 Ctl, it should be noted that in the in vitro experiments presented on page 12 of the specification, the advantage of the chimeric molecule of the invention probably is not demonstrated to its full extent, as the benefits of targeting of the chimeric molecule of the invention to particular cells are not evident in vitro in the absence of non-target cell types.

The Examiner appears to be suggesting that a combination has been made between the known antibody-cytotoxin concept and the known MHC class I/II cell system for processing/association and that this combination is not inventive. Such a combination does not lead to the invention as claimed; and, any suggestion that the combination, insofar as it may result in the invention as claimed, is not inventive, cannot properly be maintained. Such a suggestion could be made only with the benefit of hindsight.

It is noteworthy, for example, that EP 0 532 090 concerns antigen presentation, but not the targeting of specific cells, whereas Murphy et al concerns the targeting of specific cells, but not the delivery of peptides to MHC molecules. Zimmerman concerns the targeting of specific cells, but not the internalization of the targeted molecule. The objectives of the studies, then, were

clearly different and there is nothing in any of the documents to suggest that their teachings could be combined, or if combined would teach a molecule or use of the invention.

On the other hand, the present invention provides classes of molecules whereby the delivery of peptides, for example, for presentation by MHC molecules, may be optimized. This allows problems with existing methods to be addressed. Delivery may be optimized by selection of the components of the molecule by means of which the peptides are delivered. For example, each component may be independently optimized by using components from different sources, as required by claim 2. Using components from different sources provides for flexibility and the ability to optimize each component to make the most efficient molecule possible for the particular application.

The molecule may have a binding portion comprising an immunoglobulin molecule or an effective portion thereof when the effector portion consists of one or more copies of an immunogenic peptide, as required by claim 1. None of the cited documents teach methods by which immunogenic peptides may be delivered efficiently to and internalized by specific cell types and there is no mention in any document of the desirability of such efficient delivery and internalization or how it could be achieved.

For example, using the methods demonstrated in EP 0 532 090 or Fawell et al, the peptides are not narrowly targeted and are therefore absorbed by a large number of cell types, as PE, for example, has receptors on most cell types and therefore does not

provide narrow targeting. Further, the molecules of Lowenadler et al do not comprise a cell targeting domain.

It is clear that an effective method for delivering immunogenic peptides or peptides exerting an immunomodulatory effect to specific target cells (either immunological cells with MHC class II or non-immunological cells, for example tumour cells) was not known in the prior art. Further, exogenously delivered peptide would not normally reach the MHC class I compartment. The chimeric polypeptides of the invention, for example as claimed in claim 6, allow presentation of the effector peptide in association with MHC class I molecules to be optimized by using components from different sources, as commented on above, in addition to allowing targeting of the effector peptide to specific target cells. The benefits of the chimeric polypeptide of the invention may be particularly evident in vivo.

It is believed that the rejection of claims 1-3 and 5-23 under 35 USC § 103(a) should be reconsidered and these claims allowed in view of the additional remarks contained in this paper. This being the case, the Examiner is respectfully requested to enter this Amendment, reconsider and allow the present claims.

As previously requested, the Examiner is requested to address replies and inquiries to the undersigned attorney (who is of record) & firm listed below as the successor in interest of HAUGEN AND NIKOLAI which no longer exists.

Respectfully submitted,

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